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EXAMINER

KEMMERER, ELIZABETH

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/941,992

Applicant(s)

ASHKENAZI ET AL.

Examiner

Elizabeth C. Kemmerer, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 124-126 and 129-131 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 124-126 and 129-131 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The appeal brief of 21 May 2007 has been received and considered. Upon further consideration, finality of the previous Office Action (mailed 21 April 2006) is *withdrawn* solely to clarify the issues for appeal, and to provide Applicant with an opportunity to respond accordingly.

35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 124-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the examiner no longer asserts that **mRNA levels** are not predictive of polypeptide levels. Therefore, the following references are no longer being relied upon to support the rejections: Chen et al., Hu et al., LaBaer, Haynes et al., Gygi et al., Lian et al., Fessler et al., Nagaraja et al., Waghray et al., Sagnaliev et al., Lilley et al., Wildsmith et al., King et al., Bork et al., Celis et al., and Madoz-Gurpide et al. The following references cited and discussed by Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher et al., Alberts and Lewin, Meric et al., Zhigang et al., Wang et al., Munaut et al. The basis of the maintained rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to isolated polypeptides comprising the amino acid sequence of SEQ ID NO: 20 with or without its signal peptide, or the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209792, wherein the nucleic acid encoding said polypeptide is amplified in lung cell carcinomas. It is noted that the phrase "wherein the nucleic acid encoding said polypeptide is amplified in lung cell carcinomas" is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity. Claims are also presented to chimeric proteins comprising the aforementioned polypeptides. The specification discloses the

polypeptide of SEQ ID NO: 20, also known as PRO341. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 21 May 2007), p. 4, beginning of arguments.

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO341 had a ΔC_t value of at least 1.0 for three out of fourteen lung tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔC_t is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔC_t is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔC_t values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

First, there are several problems with the data provided in this example. Only three out of the fourteen lung cancer samples tested positive. Therefore, if a sample

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were taken from an individual with lung cancer for diagnosis, ***it is more likely than not that this assay would yield a false negative result.*** Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy **before** the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium and does not correct for aneuploidy. Thus it is not clear that PRO341 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO341 is a diagnostic probe for lung cancer unless it is clear that PRO341 is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of lung tumor samples had tested positive, the data have no bearing on the utility of the claimed PRO341 *polypeptides*. In order for PRO341 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO341 mRNA or PRO341 polypeptide levels in lung tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between mRNA levels and polypeptide levels. A specific example of the lack of correlation between

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genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

“An analysis of *WISP-1* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP-3* RNA was seen in the absence of DNA amplification. In contrast, *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient.”

See p. 14722, second paragraph of left column; pp. 14720-14721, “Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors.” Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that “Protein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph1 template” (see abstract).

The *general* concept of gene amplification’s lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Hittelman also speaks to this issue. Again, the data in the specification were not corrected for such aneuploidy events. Furthermore, Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) speak to general lack of correlation between gene amplification and mRNA/protein overexpression. The abstract of Godbout teaches “The DEAD box gene, *DDX1*, is a putative RNA helicase that is co-amplified with *MYCN* in a subset of retinoblastoma

(RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.*** (emphasis added).

The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state ***"It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added).

There is no evidence in the instant application that PRO341 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the genomic DNA including the gene being studied gene is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-

2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma.*" Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the protein has biological relevance in cancer. There is no such evidence for PRO341.

Therefore, data pertaining to PRO341 genomic DNA do not indicate anything significant regarding the claimed PRO341 polypeptides. The data do not support the specification's assertion that PRO341 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO341 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO341 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO341 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation

into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (*Pennica et al.*, *Konopka et al.*, *Sen*, *Hittelman*, *Godbout et al.*, and *Li et al.*, all of which are of record and have been previously discussed), the rejections are properly maintained.

Applicant's arguments pertaining to the remaining issues (Appeal Brief, 21 May 2007) have been fully considered but are not found to be persuasive for the following reasons.

Applicant's detailed arguments begin at p. 7 of the appeal brief. Applicant begins with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 10 of the brief, Applicant reviews Example 170, and refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 24 October 2003 is insufficient to overcome the rejection of claims 124-126 and 129-131 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in

the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.173 to 2.514-fold amplification of the gene encoding PRO341 in three lung tumors is significant. The significance can be questioned based on the absence of factual support for the expert's opinion. In the instant case, the facts are that eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO341, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Hittelman, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

Applicant argues that the PRO341 gene is an important diagnostic marker to identify malignant lung carcinomas even when the lung malignancy associated with the PRO341 molecule is a rare occurrence. Applicant urges that evidence has been provided that the PRO341 polypeptide is significantly amplified in certain types of lung carcinoma tumors and is therefore a valuable diagnostic marker for identifying certain types of lung carcinomas. This has been fully considered but is not found to be persuasive. First, Applicant is incorrect with regard to the facts. It is important to clarify that no evidence has been brought forward to establish that the PRO341 **polypeptide** is amplified in any lung tumors. The only evidence directly related to PRO341 is found in Example 170 of the specification, which indicates that PRO341 **gene** is amplified in three out of fourteen lung tumors as compared to a pooled blood DNA sample. Secondly, the PRO341 gene was not amplified in eleven out of fourteen lung tumor samples, thus establishing that it is more likely than not that a lung sample from a patient suspected of having lung cancer will yield a false negative result in the disclosed assay. While it is true that markers for rare cancers are valuable, they are only valuable if the rare tumor is adequately described and distinguished from other tumors. Applicant stated in the arguments that PRO341 is amplified in "certain types of lung carcinoma tumors." However, the specification and evidence of record do not establish which certain types these lung carcinomas are. Additionally, even if it could be established that PRO341 gene is significantly amplified in lung carcinomas, it does not follow that PRO341 polypeptide would also be over-expressed and thus useful as a cancer diagnostic molecule, for reasons discussed extensively on the record.

Applicant points to the statement in Example 170 that gene amplification is associated with overexpression of the gene product, thus allegedly indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers and diagnostic determination of the presence of those cancers. This has been fully considered but is not found to be persuasive. Substantial evidence has been brought forth to establish that it is more likely than not that gene amplification is not associated with overexpression of the encoded protein.

Applicant relies on Orntoft et al., Hyman et al., and Pollack et al. as evidence that gene amplification increases mRNA expression in general. This has been fully considered but is not found to be persuasive. Orntoft et al. used the CGH method to look at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. However, Orntoft et al. do not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO341 in the instant specification. That is, it is not clear whether or not PRO341 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al. does not support utility and enablement of the claimed polypeptides. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not

investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO341 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant refers to the Polakis declarations of 07 July 2004 and 30 March 2006. The Polakis declarations under 37 CFR 1.132 filed 07 July 2004 and 30 March 2006 are insufficient to overcome the rejection of claims 124-126 and 129-131 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because the declarations focus on the question of whether or not mRNA levels are predictive of protein levels. As explained above, the examiner is no longer arguing this point. Since the Polakis declarations do not address the question of whether or not amplified genomic DNA is predictive of increased polypeptide levels, they are no longer considered pertinent to the rejection.

At the bottom of p. 13 of the brief, Applicant argues that over 100 references have been submitted to support the asserted utility. This has been fully considered but

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is not found to be persuasive, as it is now factually incorrect. The vast majority of these references speak to the question of whether or not mRNA levels are predictive of protein levels. As explained above, the examiner is no longer arguing this point. Therefore, most of the references relied on by the Applicant are not longer relevant to the main basis of the rejections.

Applicant refers to the Ashkenazi declaration of 24 October 2003 as establishing that a polypeptide encoded by an amplified gene would still have utility even if the polypeptide itself were not overexpressed, because the absence of gene product overexpression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. While it may be true that lack of overexpression of a gene product can also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO341 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO341 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO341. No evidence has been brought forth on the record as to whether or not PRO341 polypeptide is overexpressed in lung tumors. Furthermore, the specification does not assert a utility for the claimed polypeptides based on the possibility that the PRO341 polypeptide is not overexpressed in lung cancer tissue. Finally, the Ashkenazi

declaration is viewed as supporting the instant rejections, since it contradicts the asserted utility in the specification at p. 539, lines 21-24:

“Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers.”

Applicant next points to Hanna and Mornin (1999, Pathology Associates Medical Laboratories) as supporting the Ashkenazi declaration's rationale of utility for the claimed polypeptides. Applicant reasons that an assay relying on both gene amplification and protein expression tests leads to a more accurate classification of the cancer and a more effective treatment of it. This has been fully considered but is not found to be persuasive because Hanna and Mornin support the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/protein overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin evidence that the level of protein expression must be tested empirically to determine whether or not the protein can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the protein level of PRO341 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed proteins is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial. Regarding Applicant's

argument that lack of protein overexpression leads to more effective categorization and treatments, the specification provides no assertion that the claimed PRO341 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO341. Therefore, significant further research would be required before such a utility were deemed substantial.

Beginning at p. 22, Applicant discusses the Orntoft et al. publication. Specifically, Applicant urges that Orntoft et al. looked at the correlation of mRNA levels and protein expression for individual genes. Applicant urges that Orntoft et al. find that there is a highly significant correlation between mRNA and protein alterations. Applicant argues that a correlation in 39 out of 40 gene examined supports their position that mRNA correlates with protein levels. This has been fully considered but is not found to be persuasive. First, the rejection is no longer based on the issue of whether or not mRNA levels are predictive of protein levels. Therefore, these findings of Orntoft et al. are no longer relevant to the rejection. Regarding the correlation of gene amplification with increased protein levels, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) Moreover, Orntoft et al. only concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO341 in the instant specification. That is, it is not clear whether or not PRO341 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al.'s results cannot be extended to the instant gene and protein.

Beginning at p. 24, Applicant addresses the Godbout et al. and Li et al. references. Specifically, Applicant argues that Godbout et al. base their statement quoted by the examiner on publications from 1987 and 1992. Applicant urges that their more recent references (Orntoft et al., Hyman et al., Pollack et al.) must be acknowledged as more accurately reflecting the state of the art. This has been fully considered but is not found to be persuasive. First, it is noted that Applicant claims priority to 1998, and thus the references of 1987 and 1992 are not completely out of date. Furthermore, Godbout et al. was published in 1998 and fully relies on the cited publications as being reflective of the state of the art. Regarding Hyman et al. and Pollack et al., it is noted that Hyman et al. also used CGH approach in their research, which is not comparable to the instant data for PRO341. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers (Orntoft et al., Hyman et al., and Pollack et al.) reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed

PRO341 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant argues that Li et al. does not support the rejection since Li et al. acknowledge that their results differed from Hyman et al. and Pollack et al., and may be due to differences in methodology. Applicant points to supplemental information accompanying the Li et al. publication indicating that genes amplified at a 1.4 copy number were considered significant, whereas PRO341 was amplified at least 2-fold. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above). Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At pp. 25-26, Applicant concludes that, based on the asserted utility for PRO341 in the diagnosis of selected lung carcinomas, the reduction to practice of the PRO341 protein sequence, the disclosure of methods for making polypeptides and chimeric polypeptides comprising PRO341 and antibodies that bind PRO341, and

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example 170 regarding the gene amplification assay, one skilled in the art would know exactly how to make and use the claimed polypeptides for diagnosis of lung carcinoma without undue experimentation. Applicant urges that, in general, DNA amplification correlates with increased expression of the encoded protein. Applicant argues that the specification shows significant amplification in three different lung primary tumors, evidence in the form of publications has been submitted to establish that a general DNA/mRNA/protein correlation exists, and declarations from experts have been provided to further support Applicant's position. Applicant concludes that the utility of the claimed PRO341 polypeptides has been achieved. Applicant stresses that absolute certainty is not required, and that it has been established that it is more likely than not that PRO341 polypeptides are overexpressed in certain lung carcinomas. This has been fully considered but is not found to be persuasive for the following reasons.

Regarding the gene amplification assay itself, it is noted that PRO341 gene was not amplified in eleven out of fourteen lung carcinoma samples. Therefore, PRO341 it is more likely than not that a lung carcinoma sample will not have amplified PRO341.

Also, the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Hittelman). Contrary to Applicant's assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Hanna and Mornin, Godbout et al., Hyman et al., and Li et al. Finally, a declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene

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amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. Since significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO341 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. In the absence of information regarding whether or not PRO341 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO341 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Conclusion

No claims are allowed.

No new rejections have been made, and no new evidence has been cited.

THUS, THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK



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PRIMARY EXAMINER